

1. A therapeutic composition comprising a first agent that targets an interleukin-15 receptor (IL-15R) and a second agent that inhibits a costimulatory signal transmitted between a T cell and an antigen-presenting cell (APC).

5 2. The therapeutic composition of claim 1, wherein the first agent comprises a substantially pure mutant IL-15 polypeptide that binds a subunit of an IL-15R.

3. The therapeutic composition of claim 2, wherein the subunit is an IL-15R α subunit.

4. The therapeutic composition of claim 3, wherein the mutant IL-15 polypeptide has a mutation at position 149 of SEQ ID NO:2.

10 5. The therapeutic composition of claim 3, wherein the mutant IL-15 polypeptide has a mutation at position 156 of SEQ ID NO:2.

6. The therapeutic composition of claim 5, wherein the mutant IL-15 polypeptide also has a mutation at position 149 of SEQ ID NO:2.

15 7. The therapeutic composition of claim 5, wherein the mutation at position 156 of SEQ ID NO:2 is a substitution of aspartate for glutamine.

8. The therapeutic composition of claim 6, wherein the mutation at position 149 of SEQ ID NO:2 is a substitution of aspartate for glutamine.

9. The therapeutic composition of claim 6 wherein the mutant IL-15 polypeptide has a substitution of aspartate for glutamine at positions 149 and 156 of SEQ ID NO:2.

20 10. The therapeutic composition of claim 2, wherein the first agent further comprises a moiety that leads to the elimination of IL-15R-bearing cells.

11. The therapeutic composition of claim 10, wherein the moiety that lyses IL-15R-bearing cells is an Fc region of an IgG molecule.

12. The therapeutic composition of claim 1, wherein the first agent comprises a substantially pure anti-IL15R antibody.

13. The therapeutic composition of claim 1, wherein the second agent comprises a substantially pure polypeptide that binds a B7 molecule.

5 14. The therapeutic composition of claim 13, wherein the B7 molecule is B7-1.

15. The therapeutic composition of claim 13, wherein the B7 molecule is B7-2.

16. The therapeutic composition of claim 13, wherein the polypeptide that binds B7 is a polypeptide comprising CTLA4/Ig.

10 17. The therapeutic composition of claim 13, wherein the polypeptide that binds B7 comprises an anti-B7 antibody.

18. The therapeutic composition of claim 1, wherein the second agent comprises a substantially pure polypeptide that binds CD28.

19. The therapeutic composition of claim 18, wherein the polypeptide that binds CD28 comprises an anti-CD28 antibody.

15 20. The therapeutic composition of claim 1, wherein the second agent comprises a substantially pure polypeptide that binds to CD40L.

21. The therapeutic composition of claim 20, wherein the polypeptide that binds to CD40L is a polypeptide comprising an anti-CD40L antibody.

20 22. The therapeutic composition of claim 1, wherein the second agent comprises a substantially pure polypeptide that binds to CD40.

23. The therapeutic composition of claim 1, wherein the polypeptide that binds to CD40 is a polypeptide comprising an anti-CD40 antibody.

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24. A method of suppressing an immune response in a patient, the method comprising administering to the patient a therapeutic composition comprising a first agent that targets an IL-15R and a second agent that inhibits a costimulatory signal transmitted between a T cell and an antigen presenting cell (APC).

5 25. The method of claim 24, wherein the patient has an immune disease, particularly an autoimmune disease, or is at risk of developing an immune disease, particularly an autoimmune disease.

10 26. The method of claim 25, wherein the autoimmune disease is a rheumatic disease selected from the group consisting of systemic lupus erythematosus, Sjögren's syndrome, scleroderma, mixed connective tissue disease, dermatomyositis, polymyositis, Reiter's syndrome, and Behcet's disease.

 27. The method of claim 25, wherein the autoimmune disease is rheumatoid arthritis.

 28. The method of claim 25, wherein the autoimmune disease is type I diabetes.

15 29. The method of claim 25, wherein the autoimmune disease is an autoimmune disease of the thyroid selected from the group consisting of Hashimoto's thyroiditis and Graves' Disease.

 30. The method of claim 25, wherein the autoimmune disease is an autoimmune disease of the central nervous system selected from the group consisting of multiple sclerosis, myasthenia gravis, and encephalomyelitis.

20 31. The method of claim 25, wherein the autoimmune disease is a variety of pemphigus selected from the group consisting of pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceus, Senear-Usher syndrome, and Brazilian pemphigus.

 32. The method of claim 25, wherein the autoimmune disease is psoriasis.

33. The method of claim 25, wherein the autoimmune disease is inflammatory bowel disease.

34. The method of claim 25, wherein the patient has acquired immune deficiency syndrome (AIDS).

5 35. The method of claim 25, wherein the patient has received a transplant of a biological organ, tissue, or cell.

36. The method of claim 25, wherein the patient has received a vascular injury.

37. The method of claim 25, wherein the patient has type II diabetes.

10 38. A method of eliminating a cell that expresses a receptor for IL-15, the method comprising exposing the cell to the therapeutic composition comprising a first agent that targets an IL-15R and a second agent that inhibits a costimulatory signal transmitted between a cell of the immune system and an antigen presenting cell.

39. The method of claim 38, wherein the cell is a cell of the immune system.

40. The cell of claim 38, wherein the cell is a malignant cell.

15 41. A method of diagnosing a patient as having a disease or condition that can be treated with the therapeutic composition of claim 1, the method comprising obtaining a sample of tissue from the patient and exposing the sample to an antigenically-tagged polypeptide that targets an IL-15R, wherein the occurrence of binding of the polypeptide to a cell in the sample indicates that the cell can be bound by an agent that targets an IL-15R
20 *in vivo* and thereby inhibited from proliferating in response to wild-type IL-15 *in vivo*.

42. A method of making a therapeutic composition comprising a mutant IL-15 polypeptide that binds a subunit of an IL-15R and a polypeptide that binds a B7 molecule, the method comprising

- 5
- (a) purifying the mutant IL-15 polypeptide from an expression system and
 - (b) purifying the polypeptide that binds B7 from an expression system; and
 - (c) combining the IL-15 polypeptide and the polypeptide that binds B7.

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